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# A Literature Review on the Production of Anti-rachitic Substances by the Irradiation Process

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# A LITERATURE REVIEW ON THE PRODUCTION OF ANTIRACHITIC SUBSTANCES BY THE IRRADIATION PROCESS.*

BY ELIZABETH PICKERING.

The development of our knowledge of the antirachitic vitamin within the past five years has been remarkable. No earlier than 1922 was differentiation made between the antiophthalmic vitamin A and the antirachitic vitamin D, occurring together in butter and cod liver oil and prior to that time and even in much literature published after that time, classed together as the fat-soluble A vitamin. Now, although we do not know the exact chemical structure of the vitamin D, we know it contains only carbon, hydrogen and oxygen and a method of synthesis has been arrived at. Simultaneously, our knowledge of the etiology of its deficiency disease, rickets, has shown advance.

Prior to the discovery that certain foods could be given antirachitic potency by irradiation with ultraviolet light, those rays had been used in the therapy of rickets. This work has been reviewed by Park (172). In some cases, eosin was administered before light treatment on the assumption that its ability to absorb ultraviolet light increased its action in the body (72). Rats fed on diets deficient in fat-soluble vitamins did not develop rickets when irradiated with light from a mercury vapor quartz lamp (178) although ophthalmia due to deficiency of vitamin A was not delayed (224). More recently, the effect of sunlight (11) and of ultraviolet light (63,156) in preventing leg weakness and rickets in poultry has been studied. The biologically active wave-lengths in sunlight were found by Luce to be below 296 $\mu\mu$ (153); by Huldschinsky to be from 289 to 320 $\mu\mu$ (128); and by Hess and Weinstock using Corning glass filters to be below 303 $\mu\mu$ or possibly 313 $\mu\mu$ (198). Similar protection of rats from rickets by much more prolonged irradiation (18 times) with Wood's light (about 365 $\mu\mu$) has also been reported (166).

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Almost simultaneously it was reported by Steenbock and Nelson (218, 226) and by Hess and Weinstock (89, 99) that synthetic rations (218), excreta (226), fats, (218), and oils (linseed and cottonseed (88, 89, 99) acquired ability to prevent or cure rickets in rats following ultraviolet irradiation for a period of $^1/_2$ to 5 hours (220). This property was soon traced to sterols contained in these materials. The antirachitic potency of such irradiated vegetable oils was found to reside in the unsaponifiable fraction of the oil (108, 109). Moreover, phytosterols isolated from this unsaponifiable matter and cholesterol were found capable of such activation. The activation of these sterols, purified by physical means, has been accomplished in thin layers of dry substance, in aqueous suspension (110) and in solution in benzene, chloroform (184), ether (53, 220), alcohol (53, 170) and in liquid petrolatum (181). The production of antirachitic activity proceeds with equal rapidity in atmospheres of air (146, 179, 211), in nitrogen (13, 112, 122, 191, 192, 194), or carbon dioxide (122). However, prolonged irradiation of sterols in the presence of air results in destruction of the antirachitic potency (192). Activation has been accomplished at much reduced temperatures (18).

The antirachitic substance so produced loses its activity quickly if kept in crystalline form (173) or in water suspension (122) but when kept in solution in oils, more particularly vegetable oils, its stability resembles that of vitamin D (79, 122). It may be destroyed by heating at 150–200° C. (124). By extraction with anhydrous liquid ammonia the active fraction (probably impure) of irradiated cholesterol was found to make up about 4% of the total and to be effective in preventing rickets in rats on a low phosphorus diet when fed in daily amounts of 2.5 mg. (115). By fractional crystallization of the activated cholesterol from 96% alcohol a substance was obtained after 4 to 6 crystallizations which was soluble in alcohol, non-precipitable by digitonin and capable of preventing rickets in quantities less than 0.5 mg. per 100 Gm. of diet (170, 171).

The rays which produce activation of food materials and sterols containing the provitamin are approximately the same as for prevention of rickets by direct irradiation of the animal (102, 220) but the more efficient rays lie below the upper limit. Heilbron (79) sets the limits as between 250 and 300 $\mu\mu$. The quanta of light of 265 $\mu\mu$ which will produce sufficient vitamin from cholesterol to cause deposition of calcium in the bones of a rachitic rat has been calculated (57).

In attempts to identify the provitamin, numerous derivatives of cholesterol and phytosterol have been irradiated. Negative results have been obtained with oxidation products: such as allocholesterol (194, 260), cholestan-4,7-diol (118, 256), cholestan-4-on-7-al (116, 256), $\alpha$-cholestantriol (206), cholesten (116), $\alpha$-cholesteryl oxide, $\beta$-cholesteryl oxide (116, 256), cholesterol ozonide (116, 256), pseudocholesten (116), cholestenon (116, 256), cholesterilen (116), hydroxycholesterol (256); with hydrogenated derivatives as dihydrocholesterol (104, 102, 122), and dihydrophytosterol (102, 104); and with isomers as $\beta$-cholesterol (116), heterocholesterol (116), $\alpha$-phytosterol (116), $\alpha$-, $\beta$-, and $\gamma$-sitosterol (96), stigmasterol (116, 195). Chlorides (116) and bromides (116) of cholesterol cannot be activated. Of the esters of cholesterol, the acetate (20, 49, 113, 192), isobutyrate (20), benzoate (20, 192) and oleate (124) have been activated; the cinnamate (20), aminacetate (116) and palmitate (48) could not be activated. None of the cholesteryl ethers tested have been capable of activation (20).

The inability to find any derivatives of cholesterol which could be activated by ultraviolet light lead to the discovery that cholesterol which had been purified by chemical means such as preparation of the dibromide and subsequent reduction to cholesterol, was incapable of being reactivated (196). Such cholesterol showed no longer the characteristic absorption spectrum of ordinary cholesterol. From this point coöperative work between Hess in New York, Windaus in Germany, and Rosenheim and Webster in England, and dealing primarily with a study of previous work with its relation to spectroscopic studies resulted in the conclusion that there existed in vegetable oils a "provitamin," which on irradiation with ultraviolet or light of shorter wave-lengths acquired antirachitic activity.

Hess and Weinstock first noted (105) a change in the absorption spectrum of cholesterol during irradiation consisting of decreased absorption (105). Anhydrous cholesterol shows only general absorption (84, 205), ordinary hydrated cholesterol purified by physical means possesses characteristic absorption bands at 293–4 $\mu\mu$, 279–280 $\mu\mu$ and 269 $\mu\mu$ (84). These bands are not shown by cholesterol recrystallized after irradiation (84) and are now known to be characteristic of an impurity which exists to the extent of about $^1/_{60}\%$ (177, 256) and which is probably ergosterol. The absorption spectrum of ergosterol has been recently investigated by several groups of workers (54, 81–86, 120, 163, 166, 167) and found to consist of absorption bands at 270 $\mu\mu$, 281.1 $\mu\mu$ and 293.5 $\mu\mu$ (163). On irradiation, absorption in the region 260–300 $\mu\mu$ disappears and new absorption appears in the region 230–260 $\mu\mu$ with a maximum at 247 $\mu\mu$. On further irradiation this band also disappears. This is in agreement with the disappearance of antirachitic potency following prolonged irradiation and indicates that the absorption band between 230–260 $\mu\mu$ is characteristic of vitamin D. Adam found the absorption spectra of acid extracts of unsaponifiable matter from cod liver oil containing vitamin D and of irradiated ergosterol to be identical (2). In attempts to identify the vitamin, the absorption spectra of several cholesterol derivatives have been determined (85, 86), of which that of cholestenone in alcoholic solution resembles that of vitamin D in that it possesses an absorption band at 243 $\mu\mu$ similar to that of vitamin D at 247 $\mu\mu$ and which disappears rapidly (86).

As a result of these experiments, it is known of the provitamin that: It has three absorption bands with a maximum at about 280 $\mu\mu$ (176, 177) which are destroyed by irradiation with concomitant appearance of antirachitic potency (84, 197).

It occurs with cholesterol and phytosterols, forming with them mixed crystals which are indistinguishable from the materials purified by physical means (256).

It forms with digitonin a digitonide (256), although the vitamin obtained from it does not (197).

It is more readily oxidized than cholesterol being totally destroyed by bromination, oxidation by potassium permanganate, and absorption by charcoal (256, 254).

It behaves chemically, physiologically and spectroscopically like ergosterol (254).

Cholesterol has one double bond in its molecule; phytosterol, sitosterol, fungisterol, etc., two double bonds; and ergosterol alone of the known sterols, three double bonds (182). Ergosterol occurs with fungisterol in ergot oil (43), and in

yeast fat. Its supply is limited at the present time. It has been recently detected in a variety of vegetable oils (79), by means of spectroscopic tests (83), and is presumably present in all oils and food products which have been shown capable of acquiring antirachitic potency on radiation with ultraviolet light. Windaus reports that 35 other sterols have been investigated, none of which showed any antirachitic action on irradiation (255).

Activation of ergosterol has been carried out in alcoholic (14) and in triolein solutions (14, 15) at temperatures of from —180 to +78° (249). It has been brought about by sunlight (198), the cathode ray (138, 140) and by ultraviolet light; the rate of activation increasing in the same order. Activation may also result in the production of fluorescence which is unrelated to antirachitic potency but due to the method of purification of the sterol (190). Various ergosterol derivatives, *i. e.*, dihydroergosterol peroxide (259), ergosterol pinacol, neoergosterol (258), and structurally related compounds as digitaligenin (199) are incapable of activation. However, the ergosterol peroxide can be reduced to ergosterol which is still capable of activation, indicating that it is the true provitamin (259). Doses of irradiated ergosterol necessary to prevent and cure rickets vary from 0.0001 to 0.002 mg. daily (70, 120, 197, 198). Bond has described (21, 23) a color test for the detection of irradiated ergosterol which is dependent on the liberation of iodine from potassium iodide and resulting coloration of starch. As peroxides result from the exposure of a great variety of oils, including mineral oil, to ultraviolet light, this test is not specific for irradiated ergosterol or even for antirachitic substances.

Irradiated ergosterol has been introduced on the market in England and in Germany under the names "Radiostol" (200) and "Vigantol," respectively. These have been used for the prevention and cure of rickets in animals (24, 119, 147, 175, 239) and in children (4, 15, 16, 59, 95, 121, 136, 180, 208, 213, 230, 240, 244, 246, 247). Bond has suggested its use for the treatment of wounds due to the bactericidal effect of its peroxide content (22).

The identification of ergosterol with the provitamin and the conclusion of Hess and Windaus that no antirachitic activation of cholesterol took place after purification through the dibromide has met, however, with some criticism. Jendrassik and Kemenyffi found (135) that fractionation of irradiated cholesterol with ethyl alcohol for three successive times did not remove the activated fraction if irradiation was repeated after each extraction. They were also able to activate cholesterol which has been brominated and reduced. They believe that the provitamin is a conversion product of cholesterol formed in the presence of water, and explain the discrepancy with Windaus' work by the fact that all his work was accomplished in anhydrous solvents. Bills, Honeywell and MacNair have also noted some degree of activability in cholesterol following bromination, which they ascribe either to cholesterol itself or to an undiscovered substance producing absorption bands noted at 135 and 304 $\mu\mu$ (19).

Brief reviews and discussions of this work on the relation between rickets, ultraviolet light and synthetic vitamin production have been published by Hess (92, 93), Hess and Weinstock (107), Heilbron (80), Beumer (12, 17), Komm (143), Vollmer (245) and Edelstein (45).

In addition to the various derivatives and isomers of cholesterol mentioned

above, numerous other compounds have been irradiated with ultraviolet light. Positive results have been obtained with:

Arachnis oil (49, 50, 150)
Bean seed oil (hardened) (40)
Betulin (48, 49)
Brain (94)
Butter fat (21, 248)
Dextrin (slight) (42, 248)
Egg yolk (186)
Excreta (168, 226)
Flour (102, 103, 104, 154, 155, 251, 248)
Hay (222)
Ivory nut oil (50)
Lanolin (110, 111)
Lard (220, 264)
Lemon juice (51, 52)
Lettuce (90, 91, 100, 103)
Linseed oil (88, 89, 91, 101, 103, 106, 248, 251)
Linseed oil (unsaponifiable matter) (108, 109)
Liver meal (slight) (167)
Milk fat (187, 188)
Olive oil (41, 91, 150, 220, 221, 248, 264)
Orange juice (157)
Sawdust (130, 132, 193)
Sesame oil (213)
Skin (55, 90, 102)
Spinach (26, 38, 102, 104)
Sunflower oil (50)
Tissue, muscle (218) lung liver (219)
Vegetables (40)
Wheat (90, 91, 100, 103)
Wheat embryo (48, 248)
Yeast, dried (94, 137) benzene extract (48)

Negative results have been obtained with:

Allyl chaulmoograte (122)
α-Amyral (116)
Apocholic acid (116)
Calcium lactate—ferric citrate (251)
Carrots (90)
Casein (40, 248)
Chlorophyl (103)
Citonella oil (102, 104)
Cocoanut oil (old) (220)
Corn (unground) (167)
Corn oil (hydrogenated) (251)
Cymene (102, 104)
Dextri-maltose (248)
Egg phosphatide (102, 103, 104)
Eosin (248)
Ether (227)
Gelatin (248)
Gluten (wheat) (248)
Glycerol (103)
Hemoglobin (103)
Hydroquinone (227)
Iron (reduced) (248)
Lecithin (141)
Linseed oil (saponifiable matter) (108)
Mineral oil (88, 91, 106, 220)
Oleic acid (102, 104, 141)
Paraffins (227)
Phloroglucin (227)
Protein (42, 227)
Red blood cells (103)
Salt mixtures (248)
Stearic acid (141)
Sugar (65, 248)
Water (distilled) (91)

It has been noted repeatedly that while fresh samples of certain vegetable oils acquire antirachitic activity on exposure to ultraviolet light, that old samples of the same oils cannot be activated. This has been demonstrated for cocoanut oil (93, 220), corn oil (42, 88, 91, 220), cottonseed oil (99, 106, 155, 220), oleo oil (220), peanut oil (189, 220). Starch has been reported both capable (42) and incapable (40) of activation. This undoubtedly depends upon the source of the starch and the degree of purity. Waltner has reported that tyrosine could be activated (248). This has been denied (141, 144).

The exposure of cod liver oil to ultraviolet irradiation results in disappearance of its normal fluorescence (1, 174) and various other changes in physical properties (1). Attempts to strengthen the oil by such irradiation in the presence of air resulted in the discovery that the antirachitic potency was not increased by brief irradiation (32, 261, 262) and in some cases was apparently decreased by more

extended exposure (1, 94, 262). Moreover, such irradiation in air may result in serious destruction of vitamin A (1, 253). Work done in the Squibb Laboratories indicates that no change in either vitamin A or D potency takes place on irradiation of cod liver oil in vacuo. Stoeltzner has claimed that the ergosterol present in cod liver oil may be activated by the addition of yellow phosphorus (228). This has not been confirmed. Cod liver oil has, however, been fortified by the addition of irradiated cholesterol (94, 173).

Exposure of lactating animals (56, 66, 126, 223) and women (114) to ultraviolet light has been shown to increase the antirachitic potency of their milk. Milk may also be exposed to irradiation with resulting increase in its potency. This is usually done by exposure of a thin layer at a distance of about 2 ft. (33, 236) from a quartz mercury vapor lamp for a period of 45 sec. (75) to $^1/_2$ hr. (33). It is likely to undergo, especially in the presence of air, a deterioration in taste probably due to oxidation of its protein (207) which is for that reason sometimes removed. Irradiation in air leads to a destruction of vitamin A (38, 234, 236) and the process is carried out by Scheer in an atmosphere of carbon dioxide (201, 202).

Dried milk has also been irradiated with resultant increase in antirachitic potency. A layer of 1 to 2 mm. in thickness (44, 69) is exposed to the lamp at a distance of about 1 ft. (44) [30 cm. (69)] for a period varying from 2 min. (44) to 1 hr. (69). Dow and Supplee have reported that no destruction of vitamin A (233) or C (231) occurs except with prolonged exposure. They have increased the calcifying properties of both summer- and winter-produced milk by irradiation (232). Irradiated milk has been used to some extent in the prevention of rickets (2, 31, 35, 71, 145). In Germany, various other irradiated materials, *i. e.*, protein-free butter fat (187, 188); plasmon (a casein-fat preparation) (65) gruels (71) and "Carnolactin" (milk-beef preparation) (74) have been used clinically.

These clinical experiments with irradiated cholesterol (97, 108), ergosterol (119, 148, 238) and milk (145) have shown that the synthetic vitamin has effects on calcification and on the calcium and phosphorus metabolism identical with those of the antirachitic vitamin of codliver oil.

The ultraviolet light for the above work (30, 220) has been obtained from sunlight, and various artificial sources such as the open carbon arc (220), the iron arc (220), and the mercury vapor lamps. Ordinary Mazda bulbs (127) emit some of the active light rays as does also Wood's light (166). The majority of the work has been done with Cooper-Hewitt Uviarc lamps with various types of burners. The Hanovia, Burdich, Hanot and Heraeus lamps have also been used. The spectra of the quartz mercury vapor lamps extends from 1850 to 14,000 Å. The ultraviolet spectra of the Hanovia (47) and of the Uviarc lamps (181) do not differ markedly. The total radiation grows rapidly with increase of voltage and depends greatly on the degree of cooling of the lamp. The intensities of the infra-red and ultraviolet grow the fastest. The energy characteristics are affected also by the dimensions of the lamp. The falling off of efficiency with age, due to vitrification and discoloration of the quartz, is not marked in the extreme ultraviolet (181). The intensity of the total radiation, as well as of the ultraviolet component, decreases to about one-half to one-third of its initial value in the course of 1000 to 1500 hours. During the first 500 hours' usage, no marked difference was observed in the proportion of ultraviolet emitted by the two types of lamps (47). The spec-

tral range of the mercury vapor lamps is discussed by Coblentz (28). Various methods of standardizing the intensity of the radiation have been proposed (5, 10, 60, 61, 142, 164, 165, 179, 252).

When it is desired to use only light of a limited wave-length, the rays are passed through suitable filters which cut out all light of other wave-lengths. These filters may consist of solutions of dyes, of gelatine films or of glass. Wratten Light Filters (gelatin) are sold by the Eastman Kodak Co., and glass filters by the Corning Glass Co., American Optical Co., Bausch & Lomb Optical Co., etc. The absorption spectra of some of these are given by Ellis (47) and the Bureau of Standards has determined the absorption spectra of a large number of glass filters (Tech. Paper 119, 148). The use of filters has been discussed to some extent by Hess and Weinstock (98, 104, 105).

Patents covering the production of vitamin D in foods and other products by irradiation methods have been granted to Goodall (64), Harriman (77), Jaeger (134), Merck (158, 159, 160, 161), Scheidt (203), Spolverini (215), Steenbock (217), Stamso (216) and Tillisch (235).

Knudson and Coolidge found (139) that exposure of rats on a rachitic diet to high voltage cathode rays did not protect from rickets in the largest doses possible on account of severe action on the animal tissues. However, they were able to activate by this means cholesterol which protected from rickets when subsequently fed to rats (139). Yeast, starch, cottonseed oil (138), and ergosterol (140) have also been activated. The minimum curative dosages for rats of ergosterol, irradiated by ultraviolet and cathode rays were 0.00002 mg. and 0.0025 mg. daily, respectively. Evidently, then, ultraviolet exposure produces more potent products than cathode ray exposure (140).

Exposure of cholesterol to Roentgen rays results first in appearance of photoactivity (76), followed by chemical change (183), oxidation (185) and destruction, especially when dissolved in chloroform, bromoform and carbon tetrachloride (36, 37). Roentgen rays produce no change in the spectrum of pure ergosterol (162) thus indicating lack of activation. Spectroscopic and biological examination of ergosterol irradiated successively by ultraviolet and Roentgen rays shows that the latter have a destructive action on vitamin D (162). It has been reported that foods irradiated with Roentgen rays are toxic as the result of vitamin destruction (67).

Closely related with the development of antirachitic potency in oils by irradiation with ultraviolet light, especially when carried out in air, is the phenomenon of photoactivity. In 1924, Hume and Smith performed some experiments which led them to state that ultraviolet irradiation of air in jars impressed on it some property which promoted increased growth in rats subsequently inhabiting those jars when fed a diet deficient in fat-soluble vitamins. This was subsequently corrected by the above authors (130) who traced the growth-promoting substance to sawdust present in the jar during irradiation; and by negative results obtained in attempts to prevent rickets in growing chicks with irradiated air (125). Air which had been

NOTE: Since presentation of this paper United States Patents covering irradiation mehotds for the production of vitamin D have been granted Steenbock (1,680,818), Pacini (1,681,120) and Chesney (1,704,173). A patent is pending on the use of the cathode ray for the same purpose.

ionized by exposure to emanations from radium bromide (27) and water containing radium bromide or ozone (106) were likewise incapable of preventing rickets in animals.

Almost simultaneously with the first reports of Hume and Smith, Kugelmass and McQuarrie observed that substances curative of rickets when oxidized (by oxygen or spontaneous autoxidation by air) produced a definite blackening of a photographic plate when screened by quartz but not by glass and concluded that ultraviolet rays were produced on oxidation (149). Similar observations have been made by others (7, 29, 78, 151, 169, 229, 241, 242, 243) especially after ultraviolet irradiation, but with the exception of Kugelmass and McQuarrie, these believed it to be due to chemical effects produced in the irradiated substance. No photographic effect could be noted on using an air-tight camera (34). Carrick has investigated the effect of exposure to irradiated cod liver oil in the development of experimental rickets in chicks (25).

Ordinary cod liver oil is photoactive (87, 241) and becomes more so on irradiation (242). The photoactivity of such irradiated substances has been ascribed to the phosphorescence of the quartz (21), to the "Russell" effect (78), or to ozone (151, 229) or hydrogen peroxide (243), organic peroxides (73) and ozonides (243). According to Vollmer and Serebrijski (243) all antirachitic materials contain photoactive substances. The photoactivity of cod liver oil is destroyed by boiling (73, 87); is increased by heating to 100° C. (87) and by exposure to sunlight (73) or to ultraviolet light (241, 263) in air or oxygen; and is not proportional to antirachitic potency (263, 7). The same facts are true of induced photoactivity of cholesterol (229). The photoactivity of various oils and other compounds both before and after irradiation has been investigated (7, 73, 78, 151, 169, 241, 242, 243, 263).

Similar investigation of the prevention of rickets in animals by exposure to irradiated sawdust has shown it to be due, not to secondary radiations (132, 152) as this photoactivity is likewise the result of a chemical fog (152) presumably peroxide (243), but to the presence therein of sterols which acquire antirachitic potency on irradiation (93).

The results of extensive work done on this problem indicate that the origin of naturally occurring antirachitic vitamin is based on the ultraviolet rays present in sunlight. Sunlight has been shown necessary for the formation of the vitamin in plant tissues (30). Tisdall has argued (237) that the vitamin produced by action of sunlight on sterols in vegetable matter and subsequently consumed by small fish is the source of antirachitic potency in cod liver oil. Although our knowledge of the production and properties of this vitamin has been greatly extended during the past few years, we as yet know little of its chemical nature. It is the opinion of Baly (6) that a vitamin is a chemical substance, which may be already known, in a state of high energy content. Since ultraviolet light is a source of energy, the recent knowledge concerning the synthesis of vitamine D seems to support Prof. Baly's views.

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